Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendments, claims 1-34 are pending in the application, with claims 1, 2, 31 and 32 being the independent claims. Claims 31-34 have been withdrawn. Claims 17, 23 and 27 have been amended; support can be found, for example, at page 5, line 12. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Information Disclosure Statement

The Examiner indicated that copending U.S. Appl. No. 08/249,819 (the '819 application), filed August 8, 1994, is unavailable for the Examiner's review at this time and thus requested that any documents cited therein to be considered by the Examiner be submitted by Applicants. Applicants inform the Examiner that all documents cited in the '819 application are believed to have been cited in the Information Disclosure Statement (IDS) and Form PTO-1449 filed February 1, 2000 in the captioned application. In the February 1 IDS, Applicants directed the Examiner's attention to the '819 application to ensure that Applicants have fully complied with the duty of disclosure.

The following documents, which were provided in the '819 application, are provided herewith for the Examiner's convenience: Burdick, D., *et al.*, *J. Biol. Chem. 267*:546-554 (1992) (AR22); Garzon-Rodriguez, W., *et al.*, *J. Biol. Chem. 272*:21037-21044 (August

1997) (AT22); and Iwatsubo, T., *et al.*, *Neuron 13*:45-53 (July 1994) (AR23). It is respectfully requested that the Examiner return a copy of the February 1 Form PTO-1449 to Applicants with indication of the Examiner's consideration of these documents.

Priority

As requested by the Examiner, the specification has been amended to update the continuing data.

Objections to the Drawings

Applicants thank the Examiner for indicating that any defects in the drawings can be deferred until the captioned application is allowed.

Double Patenting Rejection

Claims 17-30 were rejected under 35 U.S.C. § 101 as alleged claiming the same invention as that of claims 17-30 of prior U.S. Patent No. 5,972,634 (the '634 patent).

Claims 17, 23 and 27 have been amended to recite "a second container means containing a *polyclonal* antibody specific for Aβ peptide" (emphasis added). Applicants respectfully request that the rejection under 35 U.S.C. § 101 be withdrawn.

Claims 1-16 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-16 of the '634 patent.

Upon favorably indication of allowability of claims 1-16 (and claims 17-30), Applicants will submit an appropriate terminal disclaimer. It is respectfully requested that the obviousness-type double patenting rejection be held in abeyance until such time.

Rejections Under 35 U.S.C. § 112

Claims 5-16 were rejected under 35 U.S.C. § 112, first paragraph, allegedly for lack of enablement. Applicants respectfully traverse.

The Examiner stated that the specification allegedly fails to teach how to predictably and reproducibly make polyclonal and monoclonal antibodies which specifically bind Aβ1-42 but do not cross-react with Aβ1-40 and vice versa. According to the Examiner, the specification fails to teach what immunogen would generate a polyclonal with the claimed properties, how to make a polyclonal with the claimed specificity, and how to make and screen for monoclonal antibodies with the claimed binding patterns.

Applicants point out that after sufficient evidence provided by Applicants, the parent U.S. Appl. No. 08/817,423 was allowed (now U.S. Patent No. 5,972,634), with claims directed to, *inter alia*, an assay using *monoclonal* antibodies which specifically bind Aβ1-42 but do not cross-react with Aβ1-40 and vice versa. The examiner of the '423 application was in fact the present Examiner. Moreover, by the Preliminary Amendment filed October 25, 1999, the claims in the captioned application are directed to an assay using *polyclonal* antibodies which specifically bind Aβ1-42 but do not cross-react with Aβ1-40 and vice versa. Thus, it is unclear to Applicants why the Examiner is referring to both polyclonals and monoclonals in the Office Action. Clarification is respectfully requested.

Attached herewith is a Declaration Under 37 C.F.R. § 1.132 ("Rule 132 Declaration"), executed by Professor Richard Strugnell, who is not an inventor of the captioned application. According to Professor Strugnell, based on the disclosure of the captioned application and the knowledge in the art at the priority date of the captioned application (October 19, 1994), one of ordinary skill in the art of preparation of monoclonal

and polyclonal antibodies could have readily generated specific polyclonals to each of Aβ1-42 and Aβ1-40 with only routine experimentation. *See*, Rule 132 Declaration. For sake of brevity, Professor Strugnell's statements, which fully addresses the technical concerns of the Examiner in the Office Action, are not repeated herein. It is respectfully requested that the Examiner consider the Rule 132 Declaration.

The Examiner cited Campbell *et al.* for the proposition that the production of polyclonal antiserum is variable and not readily reproducible. Applicants point out that the variability and reproducibility of polyclonal antiserum discussed in Campbell *et al.* are merely routine aspects that one of ordinary skill in the art deals with in generating polyclonals. *See*, Rule 132 Declaration, ¶¶ 15-16. The polyclonals generated could easily be assayed for specificity to Aβ1-40 or Aβ1-42 with only routine experimentation. *See*, Rule 132 Declaration, ¶¶ 17-18. Professor Strugnell himself has been producing polyclonals for over 20 years. *See*, Rule 132 Declaration, ¶ 3. Thus generating polyclonals is a well established technology. According to Professor Strugnell, it is a "straightforward process" that is reliable. *See*, Rule 132 Declaration, ¶ 15. Professor Strugnell has cited a few of the publications in the art that outlines methods for improving the specificity and affinity of polyclonals. It should be noted that the claims require polyclonals specific for Aβ1-40 or Aβ1-42 but does not specify the amount of affinity.

The Examiner stated that it is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of the invention in order to constitute adequate enablement, citing *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001-1007 (Fed. Cir. 1997). The Examiner stated that "[e]ven though the methods of making antibodies are

routine, in the instant case the starting materials (immunogens), nor the appropriate screening methods are provided for in the specification or the prior art."

Applicants point out that the gist of the claimed invention is briefly described as follows in the captioned application, at page 4, lines 15-28:

> It has now been found that Aβ strongly and specifically binds zinc and copper in a pH dependent manner. These binding properties of Aβ have been exploited in this invention to create *a novel means of capturing Aβ from biological fluids with a zinc- or copper-treated microwell plate*, as well as a novel means for the bulk chromatographic purification of Aβ from biological fluids.
>
> An advantage of this new ELISA technique over the previously described double antibody capture ELISA is that *it obviates the need for a capture antibody (saving reagents and expense) and, because zinc- and copper-mediated capture appears to be more efficient than immobilized antibody capture, it is over an order of magnitude more sensitive than the reported sensitivity of double antibody capture ELISA*. Hence, the assay results with biological fluids can be achieved using cheaper chromogenic substrates, in conjunction with a visible-light microwell plate reader.

(Emphases added.) Thus, the captioned application does provide the novel aspects of the invention in order to constitute adequate enablement. The claimed assay method, which is fully described in detail throughout the captioned application, is the novel and nonobvious aspect of the invention, not the antibodies per se.

In *Genentech*, the patented invention was directed to a method of producing a protein consisting essentially of amino acids 1-191 of human growth hormone (hGH) by expressing the hGH conjugated to an additional amino acid sequence which is specifically cleavable by enzymatic action and cleaving extracellularly the conjugate protein by enzymatic action to produce the hGH protein. *Id.* at 1002-03. Noting that this technique is known as cleavable fusion expression, the Federal Circuit stated that the specification does not describe a

specific material to be cleaved or any reaction conditions under which cleavable fusion expression would work. *Id.* at 1004. The Federal Circuit stated the patentee's witness did not discuss the experimentation needed for the creation of DNA coding for more *extensive* sequences, such as those that have proved necessary for the production of hGH via cleavable fusion expression. *Id.* at 1005. The enzyme mentioned in the specification in fact was taught in the art as not working well to produce hGH, and no one had been able to produce *any* human protein via cleavable fusion expression as of the application date. *Id.* at 1005-06.

In contrast, in the present case, first, the starting materials Aβ1-40 and Aβ1-42 and their sequences were well known in the art. As explained by Professor Strugnell, one of ordinary skill could have identified and generated immunogens based on the knowledge in the art. *See*, Rule 132 Declaration, ¶¶ 9-14. "The amino acid sequences of both amyloid $\beta_{1\text{-}40}$ and amyloid $\beta_{1\text{-}42}$ were also known at the priority date. As the two sequences differed only by two amino acid residues at the carboxyl terminus, a person of ordinary skill in the art would have known that it would be the carboxy end of these molecules that would bear the respective unique epitopes." *See*, Rule 132 Declaration, ¶ 12. The sequences of Aβ1-40 and Aβ1-42 are only 40 and 42 amino acids long, respectively, and the first 40 are identical! Thus, it would not have even required labor intensive, routine screening to identify the immunogens. Second, methods of generating antibodies were routine, as even admitted by the Examiner in the Office Action, at p. 7, line 7. *See*, Rule 132 Declaration, ¶¶ 14-16. Third, it would have been routine to determine whether the polyclonals generated were specific for Aβ1-40 or Aβ1-42. *See* Rule 132 Declaration, ¶¶ 17-18. In contrast to the facts in *Genentech*, wherein the Federal Circuit noted that no one had been able to produce *any* human protein via cleavable fusion expression as of the application date, polyclonals

specific for the target antigens were practiced in the art prior to the priority date of the captioned application. Thus, it is clear that the facts in the captioned application is different than the facts in *Genentech* and routine techniques, such as generating specific polyclonals, known in the art need not be disclosed in the specification.

In view of the above, it is clear that the claimed invention is fully enabled and thus the rejection under 35 U.S.C. § 112, first paragraph, should be withdrawn.

Citation and Discussion of Other Art

Applicants note the Examiner's citation of the following additional art: Reynolds, R.A., U.S. Patent No. 4,504,585 (AA1), Voller, A. and Bidwell, D.E., "Enzyme immunoassays," in *Alternative Immunoassays*, Collins, W.P., ed., John Wiley & Sons, Ltd., New York, NY, pp. 77-86 (1985) (AT23), and Bush, A.I. *et al., J. Biol. Chem. 269*:12152-12158 (April 1994) (AS3).

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Judith U. Kim

Judith U. Kim
Attorney for Applicants
Registration No. 40,679

Date: October 3, 2001

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934
(202) 371-2600

Version with markings to show changes made

A new paragraph has been added after the title at page 1 of the specification.

17. (once amended) A kit for carrying out the assay of claim 1 or 2, which comprises a carrier means compartmentalized in close confinement therein to receive one or more container means which comprises a first container means containing a solid support having a heavy metal cation immobilized thereon and a second container means containing a[n] polyclonal antibody specific for Aβ peptide.

23. (once amended) A kit for carrying out the assay of claim 1 or 2, which comprises a carrier means compartmentalized in close confinement therein to receive one or more container means which comprises a first container means containing a solid support having a heavy metal cation immobilized thereon and a second container means containing a labelled polyclonal antibody specific for Aβ peptide.

27. (once amended) A kit for carrying out the assay of claim 1 or 2, which comprises a carrier means compartmentalized in close confinement therein to receive one or more container means which comprises a first container means containing a solid support having a heavy metal cation immobilized thereon and a second container means containing a[n] polyclonal antibody specific for Aβ peptide bound to a labelled anti-antibody.